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CENTRAL EFFECTS OF DOPAMINE ON VASOPRESSIN RELEASE IN THE NORMALLY HYDRATED AND WATER-LOADED RAT

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SUMMARY

1. The effect of intracerebroventricular (I.C.V.) micro-injections of dopamine on vasopressin (AVP) release was investigated in normally hydrated and hydrated rats anaesthetized with urethane, hormone concentrations being determined by radioimmunoassay.

2. Dopamine given in doses of less than 25 μg had little effect on AVP concentrations already elevated as a result of anaesthesia and surgery. Doses of over 25 μg produced a transient increase in AVP concentrations followed by a fall. Both the increase and the fall were statistically significant.

3. Pimozide (400 μg/kg) blocked the fall in AVP concentrations following dopamine. A fall was still seen after the administration of haloperidol (400 μg/kg) but it was only significant 20 min after the injection of dopamine. The changes in AVP concentration after the administration of naloxone (400 μg/kg) were not statistically significant.

4. In water-loaded rats I.C.V. micro-injections of dopamine produced a dose-dependent antidiuresis over the range 1–25 μg. An injection of 25 μg dopamine in these animals produced an increase in AVP concentrations to $1{\cdot}8 \pm 0{\cdot}51$ μu./ml and a fall in urine flow which could be approximately matched by an infusion of vasopressin of 15 μu./min.

5. The antidiuresis in response to dopamine could be blocked by haloperidol.

6. The response to dopamine in the anaesthetized animals depends on a number of factors including the initial activity of the neurohypophysial system.

INTRODUCTION

The role of catecholamines in the release of vasopressin has been of interest for some considerable time (Forsling, 1976). The distribution of aminergic neurones is certainly suggestive of a role, since they have been shown to terminate in the region of the supraoptic nucleus and median eminence, as well as the neural lobe (Bjorkland, Falck, Nobin & Stenevi, 1974). More recently a relationship has been described between the monoamine- and neurophysin-containing pathways (McNeill, Hoffman & Kozlowski, 1977).

Studies on the nature of the vasopressin (AVP) response to dopamine have yielded

conflicting results. These may depend to a certain degree on the nature of the preparation employed. Thus Bridges, Hillhouse & Jones (1976) employing a rat hypothalamus preparation containing the supraoptic nuclei, paraventricular nuclei, median eminence and proximal pituitary stalk found dopamine increased hormone release. Further evidence for a stimulatory effect of dopamine came from Moos & Richard (1982), who found that intracerebroventricular (I.C.V.) injections of dopamine produced increased activity of depressed 'vasopressinergic' neurones, and from the observations of Urano & Kobayashi (1978) and Stutinsky (1974), who found that stereotaxic injections into the supraoptic and paraventricular nuclei or I.C.V. injections of dopamine produced an antidiuretic response. Using yet another technique, namely depletion of brain catecholamines with 6-hydroxydopamine, Miller, Handelman, Arnold, McDonald, Molinoff & Schrier (1979) also reported an excitatory effect of dopamine on the osmotic release of vasopressin in the rat. In contrast, Moss, Dyball & Cross (1971) found a reduction of electrical activity of magnocellular neurones following ionophoretic application of dopamine. An inhibitory effect of dopamine was also reported by Wolny, Plech & Herman (1974), who gave I.C.V. injections into the conscious animal, and by Cadnapaphornchai, Taher & McDonald (1977), who, in common with others, found that intravenous infusion of dopamine produced a diuresis. Still other groups of workers claim that dopamine does not affect vasopressin release. Neither Ruoff, Gosbee & Lederis (1974), investigating the response of the rat neural lobe *in vivo*, nor Hoffman, Phillips & Schmid (1977), giving I.C.V. injections, nor Kendler, Weitzman & Rubin (1978), studying man, could find any evidence of a role for dopamine in the control of AVP secretion. In addition Ball, Tree, Morton, Inglis & Fraser (1981) only observed release of AVP if the dopamine infusion produced vomiting.

In many of the *in vivo* studies no direct estimate of plasma AVP was made; instead the renal response of the experimental animal was monitored. However, urine flow is not always a good index of concurrent AVP concentrations (Forsling & Ullmann, 1975). A series of experiments has therefore been performed in which the effect of I.C.V. injections of dopamine on both plasma AVP concentrations and urine flow in the rat have been measured. A preliminary report of part of this study has been presented to the Physiological Society (Forsling & Williams, 1983).

METHODS

Experimental preparation

The experiments were performed on male Sprague Dawley rats weighing 225–275 g, given a water load of 24 ml/kg body weight and then anaesthetized with urethane administered in a dose of 1·5 g/kg body weight. The trachea was cannulated with a polythene cannula (external diameter 2·30 mm) and one carotid artery and jugular vein with catheters of external diameter 0·96 mm. A guide cannula (length 26 mm, external diameter 0·81 mm and internal diameter 0·51 mm) was stereotaxically placed above the third ventricle and fixed in position with dental acrylic cement. All wounds were sutured. The animals were placed on their sides on a sloping table and blood pressure recorded from the carotid artery with a pressure transducer (Bell and Howell). Thirty minutes after completion of surgery a blood sample of 0·8 ml was removed for the determination of the AVP concentration. After a further 20 min a micro-injection of a solution of 5 μl of the substance under investigation was given I.C.V. through a cannula (dental needle for injection, 30 g, length 29·0 mm) which was led down a guide cannula into the third ventricle. Further blood samples were then taken at either $\frac{1}{2}$, 1, 2, 5, 10 or 20 min after the injection, with a maximum of three blood

samples being removed per animal. Such a sampling regime has been used in previous studies (Aziz, Forsling & Woolf, 1981*a*) and has not been found to stimulate AVP release. Anaesthesia was supplemented when necessary by intravenously administered doses of urethane. The position of the ventricular catheter was confirmed at the end of the experiment by micro-injection of Evans Blue dye. In a number of animals prepared as described above, urine flow was also recorded via a catheter introduced into the bladder, using a drop recorder and a Devices pen recorder (Forsling, Jones & Lee, 1968). These animals were given an additional water load of 16 ml/kg and hydration was maintained by a continuous infusion of 0·1 M-NaCl infused at a rate of 0·13–0·2 ml/min. The response to I.C.V. injections of dopamine was matched by infusing AVP at rates of 2·5–40 μu./min.

Drugs administered

Dopamine (Sigma) was administered in a solution of 0·15 M-NaCl in doses of 1–50 μg.

Haloperidol (Searle) was injected in a dose of 400 μg/kg 15 min before subsequent I.C.V. injection of dopamine. Bridges *et al.* (1976) found this dose blocked the AVP response to dopamine.

Pimozide was generously donated by Janssen Pharmaceuticals Ltd. (Marlow, Bucks.) and was given in a dose of 400 μg/kg in a solution of 0·01 M-acetic acid as described by Bridges *et al.* (1976).

Naloxone hydrochloride (Narcan, Winthrop Laboratories) was given in a dose of 400 μg/kg body weight 5 min prior to the I.C.V. injection of dopamine. This dose was found to block the AVP response to morphine (Aziz *et al.* 1981*a*).

Determination of plasma vasopressin

Plasma AVP was determined by radioimmunoassay after prior extraction with bentonite (Strömberg, Forsling & Åkerlund, 1981) and using a specific antibody (Aziz *et al.* 1981*a*). Synthetic AVP (400 i.u./mg, Ferring A.B., Malmö, Sweden) was used for the iodination of AVP by the solid-phase lactoperoxidase method. The standard preparation was the First International Standard for vasopressin (77-501).

Statistical analysis

The results are presented as mean $\pm$ S.E. of mean and the values were compared using Student's t test. If the P value was greater than 0·05 the difference between the two groups was regarded as significant.

RESULTS

The effect of I.C.V. micro-injections in normally hydrated rats

The I.C.V. injection of 5 μl 0·15 M-NaCl alone had no immediate effect on the circulating concentrations of AVP which initially were 16·4 $\pm$ 1·4 μu./ml; neither were there any changes at 10 and 20 min, the concentrations being 15·2 $\pm$ 1·6 and 15·9 $\pm$ 1·8 μu./ml respectively. Injection of 0·01 M-acetic acid into the ventricle was also without significant effect on AVP concentrations.

The vasopressin response at 10 and 20 min to increasing doses of dopamine is shown in Fig. 1. No significant change in AVP concentrations was seen following the injection of 2·5 μg dopamine. Similarly the values of 15·6 $\pm$ 3·1 ($n = 9$) and 17·5 $\pm$ 0·9 ($n = 9$) μu./ml seen 10 and 20 min after injection of 10 μg dopamine were not significantly different from the control value ($P < 0·1$). When the dose was increased to 25 μg a significant inhibition was seen at both 10 and 20 min ($P < 0·05$). This reduced plasma AVP concentration was also obtained when a dose of 50 μg was injected. These changes in hormone concentration did not appear to be produced by the observed changes in blood pressure, as with 25 μg dopamine there was an initial increase in blood pressure of about 8% followed by a progressive fall so that by 10–15 min after the injection the blood pressure had returned to control values or fallen a little below. Similar changes were seen after the injection of 50 μg dopamine, but no change was seen following the injection of 0·15 M-NaCl. When the course of

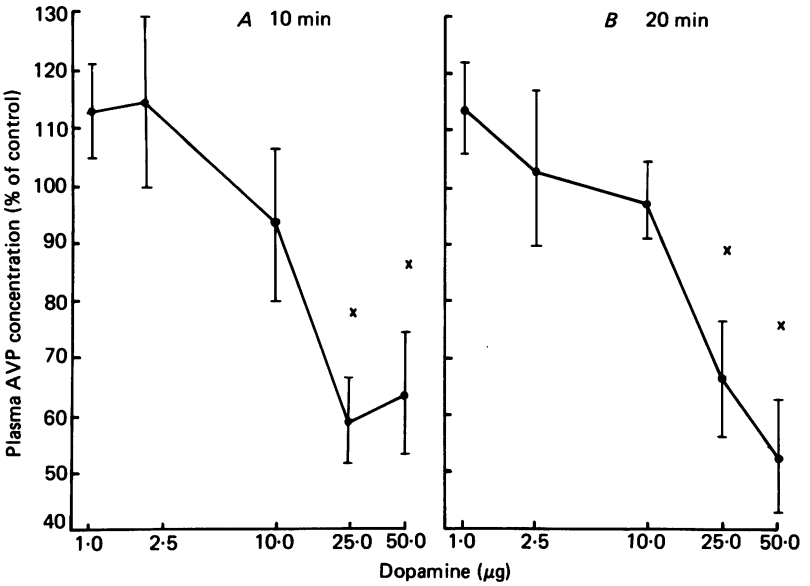

Fig. 1. The percentage fall in AVP concentrations seen *A*, 10 min and *B*, 20 min after I.C.V. injection of dopamine. The values for doses of 2·5 and 50 μg are the mean of six observations. The vertical bars indicate the S.E. of means. The points indicated (×) are statistically lower ($P < 0.05$) than the saline-injected controls.

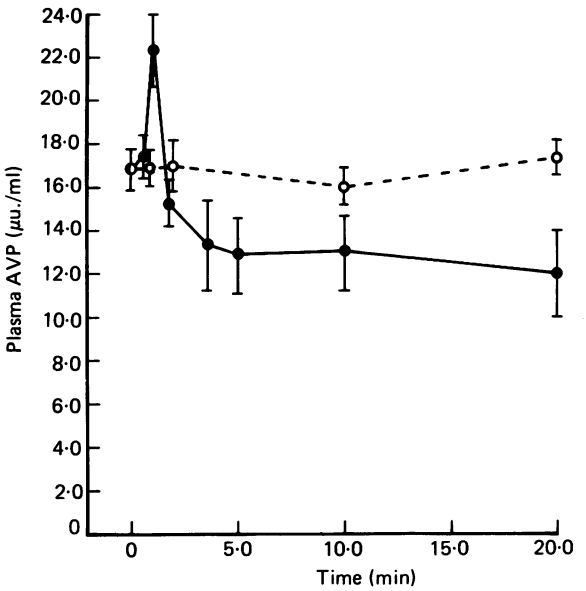

Fig. 2. Effect on plasma AVP concentrations of 25 μg dopamine given I.C.V. Each value represents the mean of nine observations; the vertical bars are the S.E. of means. The saline controls are represented by open circles and dashed lines ($n = 6$). Statistically significant changes occur at 1 min and at 10 and 20 min.

the response to 25 μg was followed in greater detail, it was found that immediately after the injection there was a transient increase in AVP concentrations. It had commenced by 30 s and was significant by 1 min. By 2 min the concentrations had fallen again, consistent with spurt release of AVP and a half-time in the circulation of 1·6 min (Forsling, Martin, Sturdy & Burton, 1973). Reduced plasma AVP concentrations were noted by 3½ min and were maintained during successive blood samplings up to 20 min (Fig. 2).

TABLE 1. Plasma vasopressin concentrations following the intracerebroventricular administration of 25 μg dopamine in the presence of either haloperidol, pimozide or naloxone. The values represent the mean of ten observations

	Plasma vasopressin concentrations (μu./ml ± S.E. of mean)		
Antagonist	Control	10 min after 25 μg dopamine	20 min after 25 μg dopamine
Haloperidol (400 μg/kg)	16·8 ± 2·1	12·8 ± 1·9	10·6 ± 2·3*
Pimozide (400 μg/kg)	14·3 ± 2·1	12·9 ± 2·2	18·1 ± 2·9
Naloxone (400 μg/kg)	16·3 ± 1·8	13·7 ± 1·9	12·9 ± 1·8

* This fall is statistically significant ($P < 0·05$).

Effect of antagonists of dopamine and opiates on the vasopressin response

Administration of haloperidol produced a transient fall in mean arterial blood pressure of 18 %, so that 15 min was allowed to elapse before the control blood sample was taken. The plasma concentration of AVP was uninfluenced by this fall in pressure, being 16·8 ± 2·7 μu./ml in the control sample. Intracerebroventricular injection of 5 μl 0·15 M-NaCl had no effect following haloperidol administration. The AVP concentrations at 10 and 20 min after the injection were 18·6 ± 2·5 and 19·3 ± 3·3 μu./ml respectively. With haloperidol no significant fall in AVP concentrations was seen 10 min after the injection of dopamine, although it was significant after 20 min (Table 1). In contrast, pimozide prevented the fall in AVP concentrations at 10 and 20 min after I.C.V. injection of dopamine. The AVP concentrations at these times were not significantly different from control values. Like haloperidol, pimozide produced a transient fall in blood pressure, which produced no change in AVP concentrations in the control plasma obtained 15 min later. A fall in plasma AVP was still obtained on I.C.V. injection of dopamine after naloxone administration (Table 1). However, the fall was only noted in four of the ten animals studied and the drop was not statistically significant over-all.

Effect of I.C.V. micro-injections in hydrated rats

Injection of 25 μg dopamine into the cerebral ventricles of hydrated rats produced a marked antidiuresis (Fig. 3). The reduction in flow was seen in the second and third minute after injection and lasted for a mean of 31·2 ± 3·6 min. The mean antidiuresis was 68·1 ± 6·7 %. Its amplitude, though not the time course, could be matched by an infusion of 15 μu./min for 15 min. The onset following injection of dopamine was more rapid, characteristic of injection of a relatively large dose of AVP (Chard & Forsling,

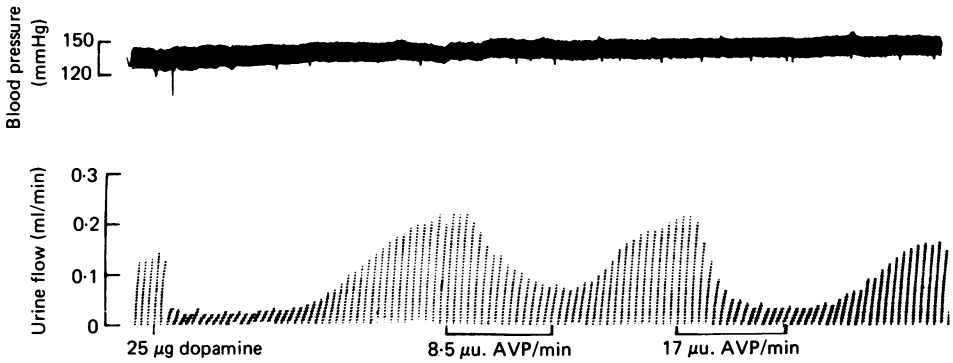

Fig. 3. The effect of I.C.V. dopamine and intravenous infusion of AVP on urine flow and blood pressure in the water-loaded rat. Each vertical line represents the volume of urine voided in 1 min.

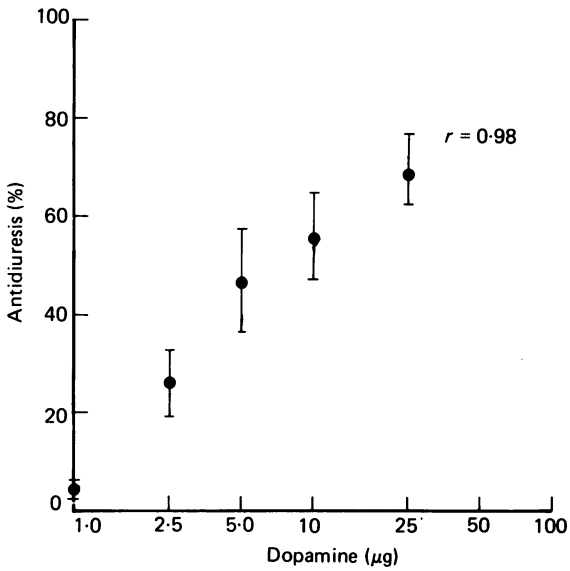

Fig. 4. Log dose–response curves for the antidiuretic response to dopamine injected I.C.V. For a straight line, $r = 0{\cdot}98$.

1976). An antidiuresis could be produced with doses of dopamine as low as 1 μg, although a response was not seen in all animal studies. A dose of 2·5 μg, however, consistently produced an antidiuresis. The magnitude of the antidiuresis obtained was clearly related to the dose of dopamine employed (Fig. 4). Although the points appear curvilinear, analysis of variance indicated that the individual values were no better fitted by a curve than a straight line. The response to 25 μg dopamine could be completely blocked by haloperidol (Fig. 5). Following injection of dopamine there was an increase in plasma AVP, concentrations peaking at 1–2 min, the values obtained at 30 s, 1 min, 2 min and 5 min being $0{\cdot}35 \pm 0{\cdot}07$ ($n = 5$), $1{\cdot}8 \pm 0{\cdot}51$ ($n = 8$), $1{\cdot}5 \pm 0{\cdot}46$ ($n = 3$) and $0{\cdot}8 \pm 0{\cdot}3$ ($n = 4$) respectively. Increases were not seen after seven

of the twenty injections; however, samples in these animals were largely taken at 30 s and 5 min. Higher concentrations were found with the infusion of vasopressin at a rate of 15 μu./min. Two and five minutes after starting the infusion plasma vasopressin concentrations had risen from $0{\cdot}16 \pm 0{\cdot}03$ to $2{\cdot}2 \pm 0{\cdot}8$ and $2{\cdot}7 \pm 0{\cdot}6$ ($n = 5$) μu./ml respectively. The concentration fell to $0{\cdot}2 \pm 0{\cdot}04$ μu./ml after stopping the infusion.

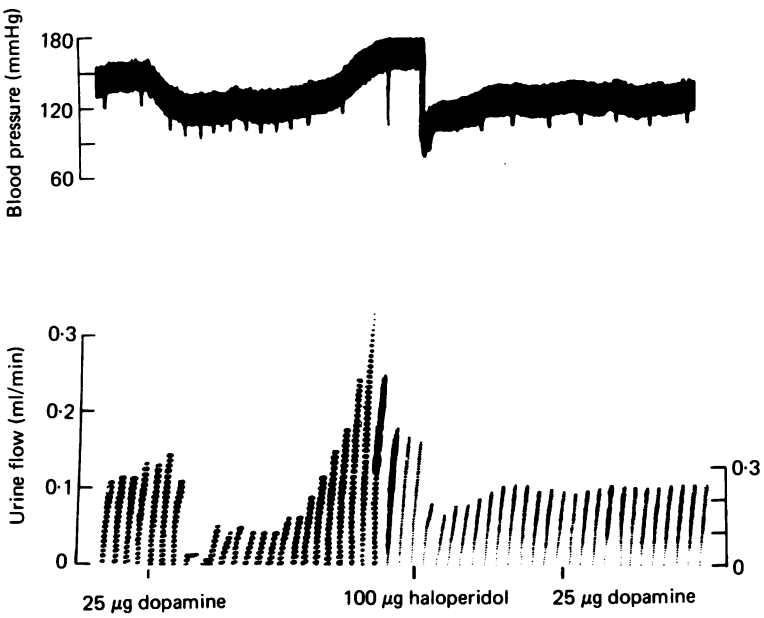

Fig. 5. The effect of haloperidol on the antidiuretic response to dopamine and on blood pressure in the water-loaded rat. Each vertical line represents the volume of urine passed in 1 min. Three minutes before the injection of haloperidol the flow recorder was adjusted; thereafter flow rates are indicated on the right-hand scale.

DISCUSSION

Central amines play an important role in modulating the release of pituitary hormones. Although interest has centred on the anterior pituitary, this is equally true of the neurohypophysial system. Histochemical evidence is consistent with a role for catecholamines in the control of secretion of posterior pituitary hormones. Histochemical fluorescence techniques have revealed a network of dopaminergic fibres in the hypothalamus (Ungerstedt, 1971), some terminating in the neurohypophysis (Björkland *et al.* 1974). Subsequently, determination of the amine content of frozen sections of brain revealed that the dopamine level in the hypothalamus is higher than the average brain level and is especially high in the median eminence (Palkovits, Brownstein, Saavedra & Axelrod, 1974).

Many approaches have been used in the investigation of the role of dopamine in the central control of neurohypophysial hormones. Experiments have been performed *in vitro* and also *in vivo* when dopamine has been given into the third ventricle, ionophoretically applied onto the cells of the supraoptic nucleus or infused intra-

venously. Furthermore, both anaesthetized and unanaesthetized preparations have been used. The various investigators have concluded that dopamine inhibits, stimulates or has no effect on AVP release. The confusion is not confined to studies on AVP. Similar conflicting results have been obtained for oxytocin and certain of the anterior pituitary hormones.

The discrepant results may be attributed in a large part to the experimental approach adopted. For example Baggio & Ferrari (1981) found that dopamine could influence water handling by the kidney, which could be important if urine flow, not AVP concentrations, were determined following systemic administration of dopamine. The response could be influenced by the initial activity of the neurohypophysial system, since it is difficult to demonstrate a fall in AVP concentrations in an animal undergoing a maximal diuresis. Equally it might be difficult to demonstrate a small increase if the circulating concentrations were already elevated. In the present investigation an effort was made to approach the problem by combining several of the approaches made by other investigators. Both urine flow and plasma AVP concentrations were monitored after I.C.V. injection of dopamine. The study employed dopamine antagonists and animals in which AVP was elevated after anaesthesia and surgery, or very low following a water load and allowing sufficient time after surgery to allow the animal to be in water diuresis. The results indicate that the nature of the response depended on the dose of dopamine employed and the time after the injection when the observations were made, as well as the nature of the preparation.

In rats not given an additional fluid load AVP concentrations were elevated shortly after anaesthesia and surgery, as previously reported (Aziz *et al.* 1981*a*; Lightman, Forsling & Todd, 1983). Injection of 25 μg dopamine into the third ventricle of these animals produced an initial transient increase in plasma AVP concentrations which did not appear to be related to the introduction of saline into the third ventricle, as saline alone produced no changes. Neither did the increase in AVP appear to be related to blood pressure, as over this time period a small increase was observed, rather than the fall which would be necessary to augment AVP release (Forsling *et al.* 1973). By 10 and 20 min after injection of doses of at least 25 μg dopamine an inhibition of vasopressin release was seen, together with a fall in blood pressure. A similar time course for the fall in AVP concentrations and in blood pressure was observed by Kimura, Share, Wang & Crofton (1981) following infusion of dopamine into the third ventricle of anaesthetized dogs. Interestingly these authors noted an increase in AVP concentrations (though not statistically significant) during the latter part of the infusion, before the fall seen when the infusion stopped.

A small change in AVP concentration was noted following I.C.V. injection of 25 μg dopamine in hydrated animals. This dose of dopamine produced an antidiuresis which could be matched by an infusion of AVP of 15 μu./min. From the clearance rates of neurohypophysial hormones (Forsling *et al.* 1973) such an infusion should produce an increase in circulating concentrations of AVP of 2·5 μu./ml. In a series of studies in which AVP concentrations were determined during infusion of the hormone, concentrations of 2·7 μu./ml were obtained, a level much higher than those seen following injection of 25 μg dopamine. It is possible that the infusion did not truly match conditions following dopamine injection or that some factor other than AVP contributed to the antidiuresis. Such a factor has been postulated by Huidobro (1980)

to account for the antidiuresis seen after I.C.V. injection of dopamine into Brattleboro rats which are unable to synthesize AVP. Whatever the underlying mechanism, however, it would appear to be a fairly specific one, as the antidiuresis observed was clearly dependent on the injected dose of dopamine and could be blocked by haloperidol.

Opiates are known to influence AVP release (Aziz, Forsling & Woolf, 1981*b*) so that it is likely that dopaminergic and opiate pathways interact in the control of AVP. Such a possibility was also raised for the control of the other neurohypophysial hormone, oxytocin, by Vizi & Volbekas (1980). The reduction in AVP release after dopamine could be blocked by naloxone, so that opiates may influence dopaminergic neurones involved in the release of AVP. The results of Lightman, Iversen & Forsling (1982) suggested that opiates could influence dopamine neurones involved in the release of AVP.

The apparent complexity of the response to dopamine is not surprising as the catecholaminergic innervation of the hypothalamus has been characterized as a complex neuronal network with catecholaminergic fibres interconnected at both their origin and terminus (Palkovits, 1981). Analysis of the response is made more difficult by (1) the observation that dopamine agonists can inhibit the firing of dopamine cells (Bunney, Aghajanian & Roth, 1973) and (2) the presence of autoreceptors on dopamine neurones (Roth, 1979). Furthermore, dopamine may act as a neuromodulator rather than a neurotransmitter (Moos & Richard, 1982). It is also possible that dopamine may be effective at the level of both the hypothalamus and pituitary. The time of onset of the response to I.C.V. injections would then depend on the time of diffusion of the drug to different sites. The stimulatory effect could be produced by dopamine acting on periventricular receptors. The ensuing inhibition might result from an action at the posterior pituitary. Lightman *et al.* (1982) found that dopamine directly inhibited AVP release from the pituitary. The dopamine agonist 2-amino 6,7-dihydroxy-1,2,3,4-tetrahydronaptholone (ADTN) reduced the release of vasopressin from the neural lobe in response to electrical stimulation, an effect enhanced in the presence of enkephalin. However, Bicknell & Leng (1982), as a result of their studies with the dopamine antagonist spiperone, found no evidence that endogenous neurohypophysial dopamine regulates AVP release.

Thus dopamine given to the third ventricle of normally hydrated, anaesthetized rats appears to give a biphasic response, namely stimulation followed by inhibition. In the hydrated animal only release was observed, although in near maximum antidiuresis inhibition would be difficult to demonstrate. Factors other than vasopressin could have contributed to the observed antidiuresis in hydrated animals.

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